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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,838	QUAX ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-17,19-21 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-17,19-21 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 8/8/05 has been entered.

Claims 2-5, 18, and 22-25 are cancelled.

Claims 1, 8-9, 12-13, 15, and 19-21 are amended.

Claims 26-29 are newly presented.

Claims 1, 6-17, 19-21, and 26-29 are presently pending and considered.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Drawings

In light of Applicant's co-submitted drawing replacements of 8/8/05, which are accepted, the objection to the drawings is withdrawn.

Claim Status: Cancelled Claims

In light of Applicant's cancellation of claims 2-5, 18, and 22-25, all rejections and/or objections to such claims are rendered moot, and thus, are withdrawn.

Claim Objections

In light of Applicant's amendments, the objection to Claim 13 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is withdrawn.

Claim 8 is newly objected to, for the limitation "bovine spienic trypsin inhibitor". There is no bovine spienic trypsin inhibitor. However, such is not a metes and bounds error, as it is believed this is typographical error introduced during the amendments.

Claim 17 is objected to for the limitation "liverspecific promoter". The correct terminology is to use two separate words, optionally separated by a hyphen, i.e., liver specific promoter, or liver-specific promoter. It is believed that this is a typographical error.

Claim 19 is objected to for the limitation "useful for transfection or transduction of mammalian, cells, wherein ...". It is believed that that this is typographical artifact error due to the amendments, and the term "cells" should not be separated by a comma from "mammalian".

Claim 20 is objected to for not requiring the particulars of the claim from which it depends. To wit, Claim 20 simply requires the nucleic acid molecule, and not the vector of claim 1, and therefore, it is improperly dependent and should be written in independent form. However, for purposes of compact prosecution, such claim will be considered to require the vector of claim 1.

Claim 20 is also objected to for the term "and wherein the dormain with an effector function...". It is believed that this is a typographical error, and Applicant intended to use the term "domain", however, "dormain" is not a word, and must be corrected.

Claim 21 is objected to for not requiring the particulars of the claim from which it depends. To wit, Claim 21 simply requires the nucleic acid molecule, and not the vector of claim 1, and therefore, it is improperly dependent and should be written in independent form. However, for purposes of compact prosecution, such claim will be considered to require the vector of claim 1.

Claim 21 recites the limitation "recovering the hybrid polypeptide or protein produced, thereby, producing the hybrid polypeptide or protein." There appears to be no necessity for placing a comma after the term "thereby", and thus such comma introduces confusion into the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-9, and 12-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "LDL receptor related protein ([alpha]2-macroglobulin receptor)". The metes and bounds of such parenthetical limitation are not clear.

Claim 15 recites the limitation "based on shuttle vector pMAD5-ATF-BPTI". The metes and bounds of such limitation are not clear. To help Applicant understand, it is unclear what modifications can be made to this vector and still have a vector of the invention.

Claim 19 recites the limitations "([alpha]2-macroglobulin)". The metes and bounds of such parenthetical limitation are not clear. To help Applicant understand, it is unclear whether this is meant to indicate to the artisan the name of the protein, or to indicate another limitation.

Claim 20 recites the limitation "([alpha]2-macroglobulin)". The metes and bounds of such parenthetical limitation are not clear. To help Applicant understand, it is unclear whether this is meant to indicate to the artisan the name of the protein, or to indicate another limitation.

Claims 6-17, 19-21, and 26-29 are rejected for depending from rejected base claims and not overcoming the lack of clarity in such base claim.

Response to Argument – indefiniteness

Applicant's argument of 8/8/05 has been fully considered but is not found persuasive.

Applicant argues that the limitation in claims 19-20 is an alternative name for LDL receptor related protein (Applicant's argument of 8/8/05, pp. 10-11, paragraph bridging).

Such is not persuasive, because it appears that such limitation is an alternative listing for the receptor associated protein that binds to LDL receptor related protein. Moreover, simply placing such limitation in the claim in the form of a parenthetical fails to demonstrate that it is a synonym for any particular protein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-17, 19-21, and 26-29 remain or are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A recombinant vector useful for transfection or transduction of mammalian cells by direct administration to thereby inhibit neointimal formation, said vector comprising a nucleic acid sequence encoding a hybrid protein or polypeptide, wherein said hybrid protein or polypeptide is operably linked to a constitutive promoter and comprises the receptor binding domain of urokinase and the protease inhibiting domain of bovine pancreatic trypsin inhibitor, does not reasonably provide enablement for any condition, any binding domain, any effector domain, any promoter, or the use of multiple binding domains and/or multiple effector domains, or any method of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 6 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claims are broad because they encompass nucleic acid molecules comprising any expressible hybrid polypeptide or protein, which hybrid polypeptide or protein comprises any domain with any binding function and any domain with any effector function. Such binding function is taught to be required to prevent system effects and/or diffusion of the hybrid protein, thereby localizing all effects to the specific tissue(s) that require such effector function (e.g., pp. 4-5, paragraph bridging). The domain with an effector function may be any function desired,

including protease, protease inhibitory, and vasoregulatory functions (e.g., p. 6, paragraphs 2-4). Moreover, the only use specifically disclosed by Applicant for such transfection/transduction of mammalian cells is to prevent cell migration (e.g., p. 1, paragraph 3). However, from the broad disclosure, it is evident that any desired function, which is also desired to be localized to a particular cell type, is encompassed by the claims (e.g., p. 4, last paragraph). The broad aspects, encompassing any binding function, any effector function, any receptor binding domain, any protease inhibitor domain, and multiple binding and/or effector domains, and being drawn generally to *in vivo* and *ex vivo* use, given the context of the specification (pp. 4-5, paragraph bridging (it is understood from this paragraph that Applicant wishes to induce local action of these expressed proteins *in vivo* and thereby avoid systemic effects, and hence, the claims, within the context of the specification, are drawn to *in vivo* and *ex vivo* use of such cells)), are not enabled for their fully claimed scope because the Artisan would have to perform undue experimentation to reasonably predict the working embodiments embraced by the claims, given Applicant's disclosure and the state of the prior art.

Specifically, with respect to making these hybrid proteins, the Artisan would not find it reasonably predictable that any particular hybrid protein would fold correctly and contain the activity required to exert its binding, as well as its effector, functions at the same levels as that of the native proteins from which these domains are obtained.

To wit, it has long been known how to mutate proteins, but it has been similarly long been known that such mutations are not reasonably predictive of activity for any particular protein. For example, Rudinger (1976) Peptide Hormones, University Park Press, Baltimore, MD., pp. 1-7 discusses the peptide hormones and the characteristics of amino acids as

components of the peptide hormones (TITLE). (It is noted that Rudinger discusses peptide hormones, but the general areas of unpredictability are common to all proteins.) In doing so, Rudinger notes that many amino acids may be grouped according to general characteristic (pp. 1-3), and many of these are also classified in two or more classifications (p. 3). Hence, simple mutations of "type" are not reasonably predictable, because there are multiple types to any particular amino acid. Moreover, Rudinger finds that the context of any amino acid is important for structure (pp. 3-4), and that therefore, simple deletions, insertions, or substitutions are also not reasonably predictable, because not only is "type" important, but context is also important, having longer-range effects than that of simply type. Further, Rudinger discusses the mechanisms of information transfer (e.g, binding and effecting a receptor, which is analogous to any protein binding anything and causing any particular effect) (pp. 4-5). In doing so, Rudinger finds that there exist "patterns" on molecules for recognition, which may involve amino acids close by in the amino-acid polypeptide sequence, or far away (Id.). As such the conformation of the whole molecule is important, and any particular amino acid change, deletion, or addition, may alter the conformation of the molecule enough to affect any particular binding and effect on another molecule.

> In analyzing the significance of such observations, Rudinger states that:
> In a given molecule, some amino acids or sequences obviously owe their 'significance' to their inclusion in the pattern which is directly involved in recognition by, and binding to, the receptor. However, the fact that the existence of this pattern is dependent on a conformation stabilized by intramolecular interactions, ..., implies that other amino acids or sequences contributing to this conformational stability will be no less 'significant' for the biological activity of the molecule.

(p. 5).

And, in conclusion, Rudinger states:

> The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study. The careful design of synthetic analogues, and their evaluation in biological systems which permit separate analysis of the various phases of hormone action, is the best way to obtaining such information.

(p. 6).

Bowie, et al. (1990) Science, 247 : 1306-10 provides similar insight into the lack of reasonable predictability for the mutation of any particular protein. To wit, Bowie discuses that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). In general, Bowie continues to reflect the observations of Rudinger: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10).

From Rudinger and Bowie, the Artisan would surmise that to carve out particular regions from any two proteins, and form a fusion protein from these regions, would not be reasonably predictable to produce a functioning protein. These proteins, their binding, and their catalytic function are all intrinsically tied to the particular context of the whole enzyme. In fact, some proteins depend on one function of the protein to activate another function, or the functions may be so inextricably linked such that merely taking the portion which maps to the particular function desired would not work (e.g., Meyer, et al. (2003) NY. Acad. Sci., 995: 200-07

(ABSTRACT); Chandrasegaran, et al. (1999) Biol. Chem., 380 : 841-48, p. 842, col. 1, paragraph 2). Hence, the Artisan would not be able to reasonably predict for any particular binding function and any particular effector function, that the hybrid protein made would actually have the desired activities.

Moreover, with respect to the desired targeting by the binding moiety, Applicant provides only a few receptor binding portions, e.g., from urokinase, from EGF, from receptor associated protein that binds to LDL receptor related protein, and VLDL receptor, but only one is shown to have an effect in chimeric form (urokinase, EXAMPLE 12). Therefore, due to the lack of reasonable predictability that any of these other receptor binding domains would even function in any particular hybrid context, and the fact that Applicant has not provided any other binding domains, the Artisan would not know what receptor binding domains would be required to localize the action of the effector domain to any particular cell or tissue type. Furthermore, because Applicant has not even described any other function except that of inhibitors of proteases, the Artisan would not know what particular function would be desirable in any particular tissue-localized effect. Next, even if such hybrid proteins were functional, they would not prevent any activity, degradation, migration, invasion, or tissue remodeling, if only for the simple reason that no inhibitor would be 100% effective. In fact, Applicant's experiments demonstrate that their only known effective hybrid protein is not 100% effective (Figure 4). On top of that, the single hybrid protein produced would not inhibit all types of proteases, and therefore, some degradation, migration, etc., would be predicted to occur by the Artisan. Also, the art recognizes that the inhibition of a single proteinase may not be enough to prevent any

particular activity (Aguilera, et al. (2003) Cariovascular Research, 58: 679-688, pp. 686-87, paragraph bridging).

Also, these problems with the activity level of the hybrid protein are compounded by the art of gene therapy. Gene therapy itself has proven time and again to be not reasonably predictable, and therefore to require undue experimentation for the practice of broad claim limiations.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many

of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression

occurs for a long enough period of time to effect treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, encoding specific hybrid proteins, under the control of specific promoters and other control elements, would overcome this showing for that specific method of administration, because, if treatment is successful, it must have met these aforementioned requirements.

Applicant's experiments however, only demonstrate a single hybrid protein to actually have an activity and to have an effect on a specific disorder: neointimal formation (EXAMPLE 12). Moreover, because these experiments were carried out in culture, where the vector could be administered directly to the cells, Applicant has only demonstrated that direct administration may be used. Furthermore, a constitutive promoter was used, and hence it is not reasonably predictable that any promoter could be used, because it is not reasonably predictable that enough protein would be produced, given the state of the art (above). The other experiments, while demonstrating the making of other hybrids, do not demonstrate any activity, much less treatment.

Hence, due to the lack of reasonable predictability in the art, the Artisan would be forced to perform undue experimentation with regard to determining which receptor binding domains to use, which effector domains to use, whether any particular receptor and effector domain would function when made into a hybrid, whether multi-domain hybrids would function, whether any particular route of administration would work, which conditions to treat with such vectors, or whether the prevention of local proteolytic activity, extracellular matrix degradation, cell migration, cell invasion, or tissue remodeling could be effected with any particular hybrid protein. Therefore, the claims are not found to be enabled for any other domains than a single BPTI protease inhibiting domain and a single urokinase receptor binding domain from urokinase,

or for any method of administration except that of direct administration, or for use in any condition other than neointimal formation.

Response to Argument – Enablement

Applicant's argument of 8/8/05 has been fully considered, but is not found persuasive.

Applicant argues broadly that the demonstration of making such proteins, the co-submitted article of Quax, et al. (2001) Circulation, 103: 562-69, demonstrate adequate enablement for the claimed subject matter.

Such is not persuasive. It is noted that Quax's disclosure demonstrates the same working example of ATF-BPTI of the Examples in a system. However, Quax does not demonstrate that any particular vector or *ex vivo* transformed cell will reach the site of action, and produce enough of an effect, for a long enough period of time to effect treatment (Official Action of 2/8/05, e.g., pp. 9-12). Nor does Quax demonstrate that any particular hybrid protein will be effective enough to have a therapeutic effect in the context of the amount of cells expressing, for the time frame that it expresses (e.g., Id., p. 9, paragraph 1). Further, Applicant's examples demonstrate making the protein, but do not demonstrate an effect, much less an effect, given the lack of reasonable predictability in the art, of inhibiting neointima formation. Simply making these proteins does not demonstrate efficacy given the doubt in the art. Moreover, if such did make the art reasonably predictable, the disclosure of Balance (below) is essentially the same as Applicant's disclosure, but directed to metastasis, rather than neointima formation, and hence, Balance would therefore anticipate all composition claims, or at least make a strong argument of obviousness.

Applicant is reminded that intended use is not considered limiting with respect to rejections under 35 USC 102 and 35 USC 103: claims drawn to compositions are anticipated by the composition, not its intended use.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In light of Applicant's amendments and arguments, the rejection of claim 13, under 35 U.S.C. 102(b) as being anticipated by WO 92/02553 to Balance, et al., filed 2 August 1991 and published 20 February 1992, are withdrawn. (These are withdrawn because Balance does not teach the use of viral vectors for transforming mammalian cells.)

Claims 1, 7-8, 13, 19, and 21 remain, and claim 11 is newly, rejected under 35 U.S.C. 102(b) as being anticipated by WO 92/02553 to Balance, et al., filed 2 August 1991 and published 20 February 1992.

With regard to claim 1, Balance teaches receptor binding domains linked to effector domains (ABSTRACT), which may be produced by transforming a host cell with a vector encoding the protein (e.g., p. 10, paragraph 1). Such binding domain may be the receptor binding domain of EGF (e.g., pp. 3-4, paragraph bridging).

With regard to claim 7, the effector domain may have any protease inhibitor activity (ABSTRACT).

With regard to claim 8 and 19, the inhibitor activity may be supplied from, *inter alia*, aprotonin (BPTI), any TIMP including TIMP-2, alpha2-macroglobulin, or any other inhibitor of a protease (e.g., pp. 4-5, paragraph bridging). Furthermore, the nucleic acid may be vector for transforming mammalian cells (pp. 9-10, paragraph bridging).

Response to Argument – anticipation, Balance

Applicant's argument of 8/8/05 has been fully considered but is not found persuasive.

Applicant argues that Balance teaches the administration of proteins, not the vector, and as such, the present rejections cannot be held by Balance (Applicant's argument of 8/8/05, p. 12, paragraph 1).

Such is not persuasive. Balance's reasons for making the vectors of the invention are distinct, but the same vectors are made by Balance as by Applicant's claims. As was previously stated, the reasons for making the composition do not matter, the composition is the composition, and therefore, Balance anticipates the claims (e.g., Official Action of 2/8/05, p. 12, last paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 14-16 remain, and claim 13 is newly, rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/02553 to Balance, et al., filed 2 August 1991 and published 20

February 1992 and U.S. Patent No. 5,518,913 to Massie, et al., filed 22 April 1994, patented 21 May 1996, for reasons of record.

As was noted above, Balance teaches the aspects of claim 1. However, as was also noted above, Balance does not teach mammalian viral vectors nor does Balance teach adenoviral vectors.

On the other hand, Massie teaches the production of recombinant proteins using conditional helper-free adenovirus vectors (TITLE). Such vectors comprise an expression cassette with a promoter (ABSTRACT) and such promoter may be tissue specific (cols. 4-5, paragraph bridging). Moreover, such vectors may be used to produce the recombinant protein by transforming human and other mammalian cells (col. 3, paragraph 3) and are advantageous for producing high levels of expression (cols. 5-6, paragraph bridging).

With regard to Claim 13, it is noted that Massie teaches adenoviral vectors, which are mammalian viral vectors.

With regard to Claim 15, it is noted that pMAD5 comprises, *inter alia*, a major late promoter from adenovirus, and Massie's vectors comprise the same promoter (col. 9, paragraph 3): hence, the vectors are based on pMAD5.

It would have been obvious to modify the hybrid protein encoding nucleic acids as taught by Balance by using them within the context of the adenoviral vectors of Massie. The Artisan would have been motivated to do so in order to obtain high levels of expression in mammalian cells. Moreover, the Artisan would have had a reasonable expectation of success because Balance had demonstrated that the hybrid protein could be made and Massie had demonstrated that chimeric proteins could be so-expressed.

Response to Argument – Obviousness, Balance/Massie

Applicant's argument of 8/8/05 has been fully considered but is not found persuasive.

Applicant argues that because Balance does not anticipate the base claims, these claims are free of the art of record.

Such is not persuasive. Balance has been shown to anticipate the base claims, as addressed above.

Claim Rejections – 35 USC § 103

Claims 1, 14, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/02553 to Balance, et al., filed 2 August 1991 and published 20 February 1992 and U.S. Patent No. 5,518,913 to Massie, et al., filed 22 April 1994, patented 21 May 1996 as applied to claims 1, 14, and 16, above, and further in view of Heckel, et al. (1990) Cell, 62: 447-56.

With regard to Claim 1, Balance teaches molecules comprising a first region which binds to a tumor cell and second region which inhibits a protease (e.g., p. 3, paragraph 3). Moreover, such region which binds to a tumor cell may bind to the urokinase receptor (e.g., p. 3, paragraph 4) and may be the N-terminal region of urokinase (e.g., p. 5, paragraph 4). Furthermore, the region which inhibits a protease may be from aprotonin, which is BPTI (p. 4, paragraph 2; Applicant's specification, p. 6, paragraph 3). Furthermore, such hybrid proteins may be produced by recombinant techniques (i.e., vectors encoding the hybrid protein) in animal cells (p. 10, paragraph 1) and using, *inter alia*, the PGK-1 promoter (p. 11, paragraph 6), which would function in mammalian cells. Lastly, Balance teaches a method of producing the hybrid molecules in a suitable host cell, by transforming the host cell with the vector (e.g., p. 10,

paragraph 1). However, balance does not teach the aspects of adenoviral vectors and the use of tissue specific promoters as in Claims 14 and 16.

On the other hand, Massie teaches the production of recombinant proteins using conditional helper-free adenovirus vectors (TITLE). Such vectors comprise an expression cassette with a promoter (ABSTRACT) and such promoter may be tissue specific (cols. 4-5, paragraph bridging). Moreover, such vectors may be used to produce the recombinant protein by transforming human and other mammalian cells (col. 3, paragraph 3) and are advantageous for producing high levels of expression (cols. 5-6, paragraph bridging).

It would have been obvious to modify the hybrid protein encoding nucleic acids as taught by Balance by using them within the context of the adenoviral vectors of Massie. The Artisan would have been motivated to do so in order to obtain high levels of expression in mammalian cells. Moreover, the Artisan would have had a reasonable expectation of success because Balance had demonstrated that the hybrid protein could be made and Massie had demonstrated that chimeric proteins could be so-expressed.

However, Balance and Massie do not teach or make obvious any specific tissue specific promoter for, *inter alia*, liver.

On the other hand, Heckel demonstrates that the albumin promoter is a well-known tissue specific promoter for liver cells (ABSTRACT; p. 452, col. 2, first paragraph).

It would have been obvious to modify vectors taught by Balance and Massie with the albumin promoter taught by Heckel. The Artisan would have been motivated to do so in order to obtain high levels of expression in mammalian liver cells. Moreover, the Artisan would have had a reasonable expectation of success because Balance and Massie had demonstrated that such

proteins could be produced and Heckel had demonstrated that the albumin promoter was specific for liver cells.

Response to Argument – Obviousness, Balance/Massie/Heckel

Applicant's argument of 8/8/05 has been fully considered but is not found persuasive.

Applicant argues that because Balance does not anticipate the base claims, these claims are free of the art of record.

Such is not persuasive. Balance has been shown to anticipate the base claims, as addressed above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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